REMARKS

Applicants thank the Examiner for the consideration of the January 11, 2005 Information Disclosure Statement and the documents cited therein. They also thank the Examiner for her helpful suggestions throughout the Office Action.

Objections to the Specification

The Examiner has objected to various trademarks used in the application. As the Examiner suggested, applicants have capitalized the marks. A generic description of the product follows the mark.

The Examiner has objected to applicants' use of hyperlinks. Applicants have amended page 4 and 18, as requested, to delete the "http://".

The Examiner has questioned the numbering of the Tables in the application. Specifically, she has said that Table 15 appears to be missing. Table 15 is at the bottom of page 67, lines 22-28.

The Claim Amendments

Applicants have cancelled claims 1-3, 5-6 and 11-16 as drawn to non-elected inventions. This claim cancellation is specifically without prejudice to applicants seeking claims to the cancelled subject matter in this application or other applications claiming priority and benefit from this application.

Claims 23-59 stand withdrawn. They are subject to future rejoinder if amended to correspond to allowed product claims.

Applicants have amended claims 4, 7, 8, 9, 17, 18, and 22. Applicants have added claims 60-65.

Applicants have, following the Examiner's suggestion, amended claims 4, 7, 8, 9, 17, 18, and 22 to explain the acronyms. *See, e.g.*, claim 4: human growth hormone (hGH). These amendments merely clarify the claims. They do not change the scope of the claims. The amendments are not new matter.

Applicants have amended claims 7, 8 and 9 to italicize "in vivo".

Applicants have amended claims 7, 8, 18 and 22 to avoid the word "about".

Applicants have amended claims 7, 8 and 22 to avoid the recitations of genera and subgenera in a single claim. Applicants reserve the right to file for and to obtain claims directed to the cancelled subject matter in this application or in applications claiming the benefit or priority of this application.

Applicants have amended claims 4 and 17 to clarify that the human growth hormone derivative is also a polyarginine-containing crystal. This amendment does not change the scope of the claims or encompass new matter.

Applicants have amended claim 7 to clarify the hGH release profile that characterizes a single administration of a crystal of this invention. This amendment is supported, for example, in paragraph 143 and Table 6. It does not narrow the claim.

Applicants have amended claim 8 to clarify the IGF-1 serum profile that characterizes a single administration of the crystals of this invention. This amendment is supported, for example, in paragraph 163, Table 18, and Figure 20B. It does not narrow the claims.

Applicants have amended claim 9 to clarify the recited bioavailability. The amendment does not narrow the claims.

Applicants have added new claims 60-65 to clarify that the crystals of claim 4 can have polyarginine co-crystallized with the hGH or complexed with crystals of hGH and that the crystals may comprise a cation. These claims are supported, for example, in paragraphs 50-60.

The Rejections

1. ***§112, Second Paragraph***

(i) Genera/Subgenera

Claims 7, 8, 10 and 22 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite because they recite genera and subgenera in the same claim. Applicants have rendered this objection moot by amending claims 7, 8 10 and 22. The amended claims do not recite genera and subgenera in the same claim.

(ii) "About"

Claims 7, 8, 10, 18 and 22 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite because they recite the term "about".

The term "about" is routinely used in patent claims. Its meaning in the context of a given claim and given range is well within the understanding of the ordinary skilled worker. To advance prosecution, applicants have, however, amended these claims to avoid use of the term "about".

2. ***§112, First Paragraph***

(i) Enablement

Claims 4, 7-10 and 17-22 stand rejected under 35 U.S.C. §112, first paragraph, because the specification does not allegedly enable the skilled worker to make

and use the invention commensurate with the scope of the claims. Specifically, the Examiner contends that, because the properties of crystals vary depending on crystallization conditions, applicants cannot claim polyarginine hGH crystals as a class. Rather, the Examiner would limit the claims to polyarginine hGH crystals made from calcium-acetate hGH crystals. Applicants traverse.

The claimed invention relates to polyarginine-containing crystals of hGH and its derivatives. These crystals are either co-crystals of polyarginine and hGH/hGH derivatives or crystals of hGH/hGH derivatives complexed with polyarginine. The crystals and compositions containing them are useful in the delivery of hGH to patients to treat a variety of hGH-related diseases. The crystals allow the hGH to be administered at longer time intervals than other hGH compositions. Just as importantly, the crystals and compositions containing them are patient friendly. They can be delivered using very small gauge syringes, thus, avoiding injection site reactions. And, they provide longer serum half lives and bioavailability.

First, and most importantly, this invention and its advantages are characterized by using polyarginine in the co-crystallization of hGH or as a complexing agent with hGH crystals. It is <u>not</u> about methods of crystallizing hGH or hGH crystals. hGH crystals were known in the prior art. *See, e.g.*, United States patents 5,780,599 and 6,117,984. Furthermore, while the Examiner is correct that conditions of producing an X-ray quality crystal can affect the crystal as it is measured with light diffraction, this invention is not about producing one single, large, appropriately shaped crystal for structural analysis. In this application, applicants teach methods of formulating hGH crystals for controlled release of hGH from its crystal lattice, regardless of what that

lattice is or how it is formed. Applicants have crystallized hGH in multiple ways as shown in the examples, and when formulated with a polycation such as polyargine, all of the formulations have improved release profiles. Thus, for both reasons, the Examiner's focus on crystallization is misplaced and the §112 rejections should be withdrawn.

Wholly apart for these misunderstandings of applicants' invention and contrary to the Examiner's assertions in the context of the alleged lack of enablement, the specification describes a large group of diverse methods to make hGH crystals. *See, e.g.*, paras. 0085-0113. These methods include many diverse conditions and crystallization buffers. All produce the hGH formulations that may be used in this invention, *i.e.*, either as co-crystallized with hGH or complexed with hGH crystals.

In addition, the specification provides a series of Examples that actually describe preparing hGH crystals. These examples use various salts – ammonium phosphates, sodium citrate, sodium phosphate, calcium acetate, calcium chloride, sodium acetate and zinc acetate. The Examples employ various alcohols: isopropanol, PEGs and ethanol. The Examples employ protamine and polyarginine. All produced hGH crystals having improved release profile in dissolution experiments. This diversity of crystallization belies the Examiner's suggestion that hGH crystallization is not predictable.

In the specific context of hGH crystals containing polyargine, the Examples likewise depict diverse conditions. Example 19 mixes sodium rhGH crystals with polyarginine. Table 16 shows that these compositions were better than soluble hGH in maintaining serum hGH concentrations in rats over time. *See also* Table 17 (The T^{max} for polyarginine complexed sodium hGH crystals was 10 hours, while that of soluble

hGH was 2 hours. And, the $T^{90\%}$ was 20 hours for the soluble hGH, while it was 74 hours for the polyarginine complexed sodium hGH). Example 21 mixes calcium acetate-PEG-hGH crystals with polyarginine. Tests in rats showed that a single administration of these crystals yielded higher serum concentrations over time than daily administration of soluble hGH. Compare Table 8 and Table 12. Example 27 crystallizes hGH with sodium acetate and polyarginine. Thus, the specification provides substantial and specific teachings that show that for use in therapeutic compositions the use of polyarginine in hGH crystallization or with hGH crystals is predictable. The specification, thus, is not only enabling only for polyarginine human growth hormone crystals made from calcium acetate hGH crystals. It is enabling for all polyarginine-containing hGH/hGH derivative crystals. Indeed, a polyarginine-containing hGH crystal product according to this invention, which is not made from calcium acetate hGH crystals, has successfully completed several Phase I clinical trials and one Phase II clinical trial and is now under development for unmet clinical and market needs.

In view of these teachings and arguments, applicants request that the Examiner reconsider her enablement rejection.

(ii) Written Description

Claims 4, 7-10 and 17-22 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written description in the specification. Specifically, the Examiner contends that the claimed genus of crystals is not sufficiently described. Applicants traverse.

As demonstrated in applicants' response to the enablement rejection, hGH crystallization is not the point of applicants' invention. Nonetheless, the specification includes an extensive description of the crystals of this invention and diverse ways of making them. Both are enough to overcome the written description rejection. Applicants had possession of the claimed invention across its full scope.

The rejection, however, is not appropriate for more fundamental reasons. First, the claimed crystals are crystals of hGH or hGH derivatives. Thus, the chemical genus is those compounds that have been crystallized. This is not a large diverse chemical genus. It is limited to "hGH". Second, there can be no dispute that hGH and hGH derivatives are well known in the art. Indeed, as described above, hGH crystals exist in the prior art. And, the specification teaches diverse ways to crystallize the prior art hGHs. Just as the availability of hGH allows one to claim a diverse set of antibodies to hGH, so should the availability of hGH allow one to claim a diverse set of hGH crystals.

Applicants request reconsideration and withdrawal of this rejection.

3. §102(b) – United States Patent 5,849,535

Claims 4 and 17 stand rejected under 35 U.S.C. §102(b) as being allegedly unpatentable over United States patent 5,849,535 (the '535 patent). Applicants traverse.

The '535 patent does not describe or suggest polyarginine-containing crystals of hGH/hGH derivatives. Indeed, the portions of the '535 patent to which the Examiner points (claims 2-5 and column 25, line 24) recite hGH derivatives and excipients not crystals.

Applicants believe that the rejection may be based on a misunderstanding of applicants' claims 4 and 17. Those claims do not recite hGH derivatives in uncrystallized form. However, to clarify the intended claim scope, applicants have amended claims 4 and 17 to recite that the hGH derivatives are also crystals. This overcomes the rejection. Applicants request that the Examiner reconsider and withdraw it.

4. ***Provisional Double Patenting***

Claim 4 stands rejected for provisional double patenting in view of claims 1, 2, 4, 7, 9 and 10 of the copending application 11/169,956. Because neither claim 4 of this application nor any of claims 1, 2, 4, 7, 9 and 10 of the copending application has issued, the filing of a Terminal Disclaimer is premature.

Applicants will file a Terminal Disclaimer, if appropriate and required, before grant of these two sets of claims.

CONCLUSION

Applicants request consideration of the amended claims in view of the foregoing remarks and allowance of those claims.

Should the Examiner feel that a telephone conference with applicants' representative would assist the Examiner, she is invited to telephone the undersigned at any time.

Respectfully submitted,

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